contacting the tissue with an agent that binds to **[a]** TGF-β;

whereby the binding of the agent to the TGF-β suppresses the deleterious accumulation of the TGF-β-induced extracellular matrix component in the tissue**[; and**

whereby the suppression of the deleterious accumulation of the extracellular matrix component treats the pathology or condition].

REMARKS

Courtesies extended to Applicants' representatives in the personal interview held May 8, 1997, are acknowledged with appreciation.

By the present communication, claim 21 has been amended, to define Applicants' invention with greater particularity. Claims 27-34 have been canceled to expedite prosecution of the remaining claims. No new matter is introduced by the subject amendments as all amended claim language is fully supported by the specification.

As a result of the personal Examiner interview, the Examiner acknowledged, in the Examiner Interview Summary Record dated May 8, 1997 (Paper No. 47; copy enclosed herewith as Exhibit A), that an agreement was reached in part regarding all pending claims. More specifically, in the Interview Summary, the Examiner states that:

> The amendments to the claims 21-25, cancellation of [claims] 27-29, and cancellation of other non-elected claims put the claims in condition for allowance pending receipt of evidence or declaration showing nexus to overcome 112[, first paragraph] rejection of [animal] model to disease. See copy of attached claims.

By the present communication, claim 21 has been amended and claims 27-30 and non-elected claims 31-34 have been canceled as suggested by the Examiner. Accordingly, in view of the Examiner's above-acknowledgment, it is respectfully submitted that each of the rejections set forth in the outstanding Office Action (Paper No. 46) have been rendered moot by the amendments submitted herewith, except for the rejection under 35 U.S.C. § 112, first paragraph, related to the nexus between animal model and disease.

The rejection of claims 21-25 and 27-30 under 35 U.S.C. §112, first paragraph, as allegedly failing to establish a nexus between the results obtained in the specification and the claimed embodiments, is respectfully traversed.

The Examiner's concern with respect to the nexus between the experimental rat model and disease is related to claim 23 directed to adult respiratory distress syndrome or cirrhosis of the liver, as set forth a page 4, last paragraph of Paper No. 46. It is respectfully submitted that the claim 21, and therefore, claim 23 have been amended, as suggested by the Examiner at p. 5, ln. 3-5 of the Office Action, "to remove the treatment/cure considerations." For example, claim 21 has been amended to require "A method of decreasing the deleterious accumulation of ECM..." as opposed to a method of "treatment"

requiring that "suppression of...ECM treats the pathology or condition." The Examiner's indication of acceptable alternative claim language is acknowledged with appreciation. Since a method of treatment is no longer claimed, it is respectfully submitted that the Examiner's concern with respect to a nexus between the animal model employed in the specification and the treatment of diseases has been rendered moot.

Nonetheless, it is respectfully submitted that the nexus is well-established in the art between the rat model employed in the specification and the human diseases characterized by the TGF-β-induced production and deleterious accumulation of extracellular matrix including adult respiratory distress syndrome and cirrhosis of the liver. For example, Border and Noble, New Engl J Med, 331:1286-1292 (provided herewith as Exhibit B), describe the role of TGF-β in tissue fibrosis and provide a relatively comprehensive review of current animal models of relevant TGF-β-related human pathologies (summarized in Table 1 at p. 1288). Since the claims have been amended to require a method of decreasing the deleterious accumulation of extracellular matrix associated with a pathology or condition...", it is respectfully submitted that a showing that cirrhosis of the liver and ARDS are associated with TGF-β-induced accumulation of ECM, as occurs in the animal model, is sufficient to demonstrate a nexus between the animal model employed and the claimed diseases.

With respect to cirrhosis of the liver, Table 1 of Border and Noble, supra, cites two publications that clearly implicate TGF-β-induced accumulation of extracellular matrix as being associated with cirrhosis of the liver (liver disease):

Castilla et al., 1991, N. Eng. J. Med., 324(14):933-940 (copy provided herewith as Exhibit C); and Nagy et al., 1991, Hepatology, 14:269-273 (copy provided herewith as Exhibit D). For example, Castilla et al., supra, discloses that since all patients with increased fibrogenic activity had increased levels of TGFβ1 mRNA, "TGFβ1 may have an important role in the pathogenesis of fibrosis in patients with chronic liver disease..." (see the Abstract and throughout). In addition, Nagy et al., supra at the Abstract, discloses that:

> Detection of transforming growth factor-β_1 in active liver diseases at the site of fibrosis suggests that transforming growth factor-β_1 might have a role in the process and progression of fibrosis during the development of the disease.

Accordingly, it is respectfully submitted that a nexus, in fact, exists between the rat animal model employed in the specification and the TGF-β-induced accumulation of extracellular matrix associated with cirrhosis.

With respect to Adult Respiratory Distress Syndrome (ARDS), Limper et al., 1992, Chest, 101(6):1663-1673 (copy provided herewith as Exhibit E), discloses that the increased expression of the extracellular matrix glycoprotein fibronectin is associated with the development of adult respiratory distress syndrome (see the Abstract and throughout). Thus, it is respectfully submitted that a nexus also exists between the rat animal model employed in the specification and the TGF-β-induced accumulation of extracellular matrix associated with ARDS.

In summary, since the claim 21 has been amended as suggested by the Examiner, it is respectfully submitted that this rejection has been obviated. Nonetheless, since a nexus exists between the rat animal model employed in Applicants' specification and the TGF-β-induced accumulation of extracellular matrix associated with cirrhosis of the liver and ARDS, it is respectfully submitted that this rejection has been overcome. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

In view of the above amendments and remarks, reconsideration and favorable action on all pending claims is respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

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